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ARTICLE

Model-based approach to identify predictors of paclitaxel-induced myelosuppression in "real-world" administration

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Abstract

Taxanes are currently the most frequently used chemotherapeutic agents in cancer care, where real-world use has focused on minimizing adverse events and standardizing the delivery. Myelosuppression is a well-characterized, adverse pharmacodynamic effect of taxanes. Electronic health records (EHRs) comprise data collected during routine clinical care that include patients with heterogeneous demographic, clinical, and treatment characteristics. Application of pharmacokinetic/pharmacodynamic (PK/PD) modeling to EHR data promises new insights on the real-world use of taxanes and strategies to improve therapeutic outcomes especially for populations who are typically excluded from clinical trials, including the elderly. This investigation: (i) leveraged previously published PK/PD models developed with clinical trial data and addressed challenges to fit EHR data, and (ii) evaluated predictors of paclitaxel-induced myelosuppression. Relevant EHR data were collected from patients treated with paclitaxel-containing chemotherapy at Inova Schar Cancer Institute between 2015 and 2019 ($n = 405$). Published PK models were used to simulate mean individual exposures of paclitaxel and carboplatin, which were linearly linked to absolute neutrophil count (ANC) using a published semiphysiologic myelosuppression model. Elderly patients (≥70 years) constituted 21.2% of the dataset and 2274 ANC measurements were included in the analysis. The PD parameters were estimated and matched previously reported values. The baseline ANC and chemotherapy regimen were significant predictors of paclitaxel-induced myelosuppression. The nadir ANC and use of supportive treatments, such as growth factors and antimicrobials, were consistent across age quantiles suggesting age had no effect on paclitaxel-induced myelosuppression. In conclusion, EHR data could complement clinical trial data in answering key therapeutic questions.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Population pharmacokinetic/pharmacodynamic (PK/PD) models are typically developed using clinical trial data of relatively homogeneous populations, often excluding special populations (e.g., the elderly).

WHAT QUESTION DID THIS STUDY ADDRESS?

We show the utility/application of a published PD model of chemotherapy-induced myelosuppression on modeling real-world data (RWD) obtained from electronic health records (EHRs) with heterogeneous population, using paclitaxel as a case study. The study also highlights the key challenges of modeling RWD and explores the predictors of paclitaxel-induced myelosuppression with an emphasis on age.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Published PK/PD models were successfully leveraged to model heterogeneous EHR data. Across all the age quantiles, the nadir absolute neutrophil counts and adjunct therapies, such as growth factors and antimicrobials, were consistent, showing that paclitaxel-induced myelosuppression is not affected by age.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The current study focuses on the insights gained by combining PK/PD analysis with RWD to answer questions related to patient care, such as dosing, specifically for special populations.

INTRODUCTION

Pharmacokinetic/pharmacodynamic (PK/PD) modeling plays a pivotal role throughout the drug development process to inform dose selection. However, PK/PD models are developed based on data collected from clinical trials, where the study population is selected through specific inclusion/exclusion criteria. For example, elderly patients are typically excluded from clinical trials, which could preclude elucidating drug effect/toxicity in this vulnerable population.[1] Thus, the generalizability of the model findings to real-world patients' post-approval is often debated,[2,3] which necessitates a prospective trial to capture treatment characteristics in a heterogeneous population during the postmarketing phase. However, given the high cost associated with this approach, relying on real world data (RWD), such as electronic health records (EHRs), is considered an alternative and promising approach. In RWD, patients' longitudinal demographic and treatment characteristics are readily available as a part of clinical care, covering a wide range of demographics (age, genetic makeup, dietary habits, etc.), disease information (disease subtypes, disease severity, comorbidities, etc.) and clinical conditions (therapeutic regimen, comedications, hospital treatment protocols, etc.).[4,5] The heterogeneity in EHR data stems from minimizing selection bias as a diverse set of patient population can access health care system. In contrast, only eligible patients can participate in clinical trials, which results in a more homogeneous patient population.[6,7]

Although EHRs may be a viable alternative, the nature of RWD may present several modeling challenges. Because EHR data are not primarily collected for research purposes, the data may be sparse, missing, or contain erroneous information.[8] Some investigators have suggested implementation of automated tools for data curation, extraction, and processing. These tools contain sophisticated algorithms to extract the required information for modeling from unstructured clinical records across huge datasets.[4] Although widespread adoption of such infrastructure is unlikely in the near term, pragmatic, team-based approaches of manual curation can be useful to address specific questions.[9] Curated EHR data containing sparse PK/PD samples across heterogeneous populations can be analyzed using established PK/PD models developed based on rich clinical trial data.[10]

There is growing interest in applying PK/PD analyses to EHR data to answer questions related to drug use specifically in special populations, such as optimizing the pediatric dosing recommendations for vancomycin and unfractionated heparin.[11,12] In addition, RWD are increasingly used to support regulatory and healthcare decision making in oncology drug development with respect to dose optimization, biomarker discovery, and providing treatment options for rare diseases.[13] For example, analysis of efficacy data from Flatiron Health

RWD led to the approval of a biweekly regimen of cetuximab. This is a convenient alternative to a weekly regimen for patients with metastatic colorectal cancer.[14] In addition, survival analysis from Flatiron Health RWD provided evidence to identify tumor mutation burden as a biomarker for patients with lung cancer treated with targeted therapies.[15] Finally, investigating the dosing and prescription patterns of palbociclib and endocrine combination therapy from medical claims and EHR data supported the approval of this regimen to treat male metastatic breast cancer, which is considered a rare disease.[16]

Paclitaxel, a microtubule-inhibiting chemotherapeutic agent, is one of the most commonly used drugs as a single agent for the treatment of breast cancer or in combination with carboplatin for the treatment of lung and ovarian cancers.[17–19] The drug exhibits nonlinear PKs in distribution and elimination and is dosed either on a weekly basis with a typical dose of 80–90 mg/m^2 or every 3 weeks schedule with a typical dose of 175–200 mg/m^2.[19–21] Myelosuppression (specifically neutrophil suppression) is a common dose-limiting toxicity of paclitaxel therapy. The original implication of PK/PD modeling of taxane therapy was a method by which doses could be titrated to safe reductions in absolute lymphocyte or neutrophil counts to maximize antitumor effects without risk of hospitalization. But the development of recombinant growth factors led to approaches that used standardized administration of adjunct therapies to reduce the myelosuppressive effects and prophylactic antimicrobials to reduce risk for fever and sepsis in the context of neutropenia rather than individualized dose reduction strategies.[20] Several studies explored the predictors of myelosuppression associated with paclitaxel with a focus on age. Some studies showed a relationship between age and myelosuppression, whereas other studies did not establish an association.[20,22–24] However, these studies have at least one of the following limitations: small sample size, especially in the elderly population, studying nonclinically oriented outcomes, lack of comparative arm, or use of univariable statistical analysis (unadjusted for potential confounders).

To elucidate the predictors of paclitaxel-induced myelosuppression in a real-world care setting, we (i) manually curated EHR data to capture actually collected data not in the original EHR and to assess standard-of-care confounders, such as growth factors administration, (ii) externally evaluated and leveraged previously developed PK/PD models in modeling paclitaxel exposures and circulating neutrophils to fit longitudinal absolute neutrophil count (ANC) data from the real-world population collected from EHRs, and (iii) evaluated predictors of paclitaxel-induced myelosuppression based on model-based clinical outcome variables.

METHODS

Data extraction and curation

Data from patients 18 years or older who received taxane-containing chemotherapy between 2015 and 2019 were retrieved retrospectively from the Epic EHR database, Clarity, at Inova Schar Cancer Institute. Extracted data contained the following routine clinical care information: demographics, medical history, chemotherapy dosing, longitudinal laboratory results, specifically ANC, vital signs, comedications, and disease characteristics. The data extraction process was laborious with five team members from a database of over 7 million observations. Privacy and security were managed by storing data onsite. Primary cancer location was determined using the earliest cancer-related International Classification of Disease-10th revision (ICD-10) code listed in the medical history. Drug names were standardized using a custom drug name dictionary. Chemotherapy was considered delivered if its status was "completed," "dispensed," "started," or "given externally."

Patients were considered eligible for analysis according to the following criteria: (i) patient's age at least 18 years old, (ii) available taxane dosing, (iii) patients with at least one ANC at baseline (baseline was considered a maximum of 7 days before initial taxane dose), and (iv) patients with at least additional two ANC during the first month of treatment. Extensive exploratory analysis (using summary statistics and graphical analysis) was performed to detect outliers, entry errors, biologically implausible values, and missing or duplicate information to prepare the dataset for subsequent modeling. A thorough graphical analysis of the individual longitudinal ANC and covariate profiles was performed in relation to the timing and dose of chemotherapy to check for anomalies, such as abnormally low or high ANC values or drastic changes in covariate values that do not match previous or subsequent values. For duplicate ANC or dosing records available at the same time, only one record was considered for the final analysis. Completely missing covariate values for any patient were imputed with the mean value for the covariate in EHR dataset, otherwise, an earlier measurement of the covariate was used for a given patient (i.e., the last recorded covariate value was carried forward). Figure S1 describes the framework and steps undertaken to analyze the EHR dataset.

The analysis considered the following criteria. Because paclitaxel was the most commonly administered of all taxanes, n-albumin-bound paclitaxel, cabazitaxel, and docetaxel treatment courses were excluded. To minimize the confounding effects of combination agents, regimens

other than single agent paclitaxel or in combination with carboplatin were excluded. Additionally, PK/PD modeling was performed exclusively on the first cycle of treatment because intrinsic risk of myelosuppression is best assessed during the first cycle when patients will typically receive the full dose,[25] with a minimum rate of dose modifications or administration of confounding concomitant medications.

To incorporate infusion duration information, the institution's known pharmacy and nursing standards for administration were used: 1-h infusion for weekly paclitaxel regimen, 3-h infusion for every 3 weeks paclitaxel regimen, and 30-min infusion for carboplatin regimen, so these were assumed for all patients based on the regimen. Exact timing of the dose was not reported, so, the dose was assumed to occur 30 min after the ANC measurement if both occurred on the same day, or 24-h after if they occurred on separate days. The study was approved by the Institutional Review Board of Inova Health System.

Pharmacokinetic modeling of chemotherapy

The PK and PK/PD models previously published by Joerger et al. and Friberg et al. were applied to fit the longitudinal ANC time profiles.[26–28] Two approaches were explored and compared to fit the data. Because paclitaxel concentration measurements are not part of the standard-of-care, in the first approach, the PK parameters were fixed using literature values, and the PD parameters were estimated. In the second approach, both PK and PD parameters were fixed according to previously reported values and post hoc individual predictions were obtained.

Briefly, paclitaxel disposition was described by a three-compartment model with saturable distribution between central compartment and the first peripheral compartment, first-order distribution between central compartment and the second peripheral compartment and saturable elimination from central compartment, as shown in Figure S2A. The technical details of the model are available in the supplementary material.

Because carboplatin was shown previously to cause myelosuppression, carboplatin exposures were also simulated and linked to ANC production.[29] Disposition of carboplatin was depicted by a two-compartment model with first-order distribution and elimination, as described by Joerger et al.[27] Figure S2B and S2C show simulated mean profiles of paclitaxel and carboplatin, respectively, after administration of the typical doses that were used in the clinical studies to develop the population PK models for both agents and they show consistency with reported exposures of both drugs.

Semiphysiologic PK/PD modeling of absolute neutrophil count

Chemotherapy exposures were linearly linked to longitudinal ANC data using a semiphysiologic PK/PD model, as described by Friberg et al.[28] (Figure S2A). The model is composed of the following parameters: baseline ANC (CIRC0), mean transit time (MTT), the individual sensitivity of bone marrow to the drug (SLOPE), and feedback constant (γ). Random effects on SLOPE, MTT, and CIRC0 parameters were assumed to follow a log-normal distribution with mean of zero and variance of ω^2. The unexplained residual error was incorporated as proportional, which was assumed to have a normal distribution with mean of zero and variance of σ^2. The model code and technical details of the model are described in the Appendices S1 and S2, respectively.

The PK/PD model evaluation included: (i) standard diagnostic plots and visual predictive check (VPC), (ii) biological plausibility of parameter estimates compared to previously reported values, and (iii) precision of parameter estimates in terms of relative standard error. Nadir ANC was computed and assessed for the degree of concordance between model-predicted and observed values.

Statistical analysis

The final PK/PD model was utilized to identify patient-specific or treatment-specific predictors of myelosuppression. The main outcome variables of interest were the random effects of PD parameters: MTT, drug slope, and model-predicted nadir ANC. The predictors included age, sex, baseline body surface area (BSA), baseline ANC, cancer location, self-reported race, regimen (weekly paclitaxel, weekly paclitaxel/carboplatin and, every 3 weeks paclitaxel/carboplatin), receiving steroids (which were administered a day before paclitaxel treatment to prevent hypersensitivity reactions), growth factors (filgrastim, tbo-filgrastim and pegylated filgrastim), or antimicrobials, baseline bilirubin level, and baseline glomerular filtration rate. To assess the association of predictors with outcomes, standard stepwise linear regression was performed, where forward and backward selection procedures were used to determine the significant predictors.[30] Model selection at each step was based on Akaike Information Criterion (AIC; $\Delta AIC \geq 10.82$; χ^2, $df = 1$, $\alpha = 0.001$). Clinical relevance of the predictors was considered during final model interpretation.

Software

Population PK/PD modeling was done using the First Order Conditional Estimation with Interaction (FOCEI) algorithm of Pumas version 2.3 (www.pumas.ai). Data preparation and graphical and statistical analyses were performed using R version 4.1.3 or higher (R Foundation for Statistical Computing) running under the RStudio interface (Free Software Foundation).

RESULTS

Patients and data

A total of 2490 patients who received taxane-containing chemotherapy were assessed and screened for eligibility for inclusion in the final analysis. Figure 1 shows the details of the screening process and the number of patients excluded at each step. The final analysis dataset consisted of 405 patients. Table 1 shows the baseline demographics and treatment characteristics stratified by age groups. Eighty-six patients (21.2%) were greater than or equal to 70 years of age and 20 (5%) were greater than or equal to 80 years of age. The cancer type was predominantly breast cancer (58.7%) followed by ovarian (8.1%) and non-small cell lung cancer (7.4%). The most common chemotherapeutic regimen for breast cancer was weekly paclitaxel (63%), every 3 weeks paclitaxel/carboplatin (48%) for ovarian cancer, and weekly paclitaxel/carboplatin (87%) for lung cancer. Reflective of the cancer patient population in this health system, 221 patients reported European ancestry, 55 were Asian, and 45 were African American. Because some patients were screened for treatment eligibility prior to coming to the institutional infusion center, 95 patients did not have pretreatment bilirubin measurements recorded in the EHRs, for these patients, mean values in the dataset were imputed for subsequent analyses.

The median paclitaxel dose in the every 3 weeks paclitaxel/carboplatin regimen was 175 mg/m^2 compared to 80 mg/m^2 in the weekly paclitaxel/carboplatin and weekly paclitaxel regimens. A total of 2274 ANC measurements were included in the analysis. Median number of ANC samples per patient was five samples (range: 3–39 samples). Mean observed nadir ANC during the first month of treatment was 2.6×10^9 cells/L in the less than 70 years age group compared to 2.8×10^9 cells/L in greater than or equal to 70 years age group. The mean nadir ANC in the every 3 weeks paclitaxel/carboplatin treatment group was 2.38×10^9 cells/L compared to 3.09×10^9 cells/L and 2.2×10^9 cells/L in weekly paclitaxel/carboplatin and single weekly paclitaxel treatment groups.

Paclitaxel – absolute neutrophil count modeling

Table S1 contains the population PD parameter estimates for the ANC model pertaining to paclitaxel containing regimens. Most PD parameters were estimated precisely with relative standard error (% RSE) less than 30%. Parameter estimates were comparable to previously reported values except for SLOPE and SLOPC which showed around 2.75- and three-fold higher values, respectively. Figures S3, S4, and 2 show the standard goodness-of-fit diagnostic plots, VPC, and individual prediction plots from representative patients across all three chemotherapeutic regimens, respectively. All diagnostic plots show adequate model performance. Figure S5 shows individual predictions using external validation approach (i.e., fixing all population PK/PD parameters using literature values). Both approaches

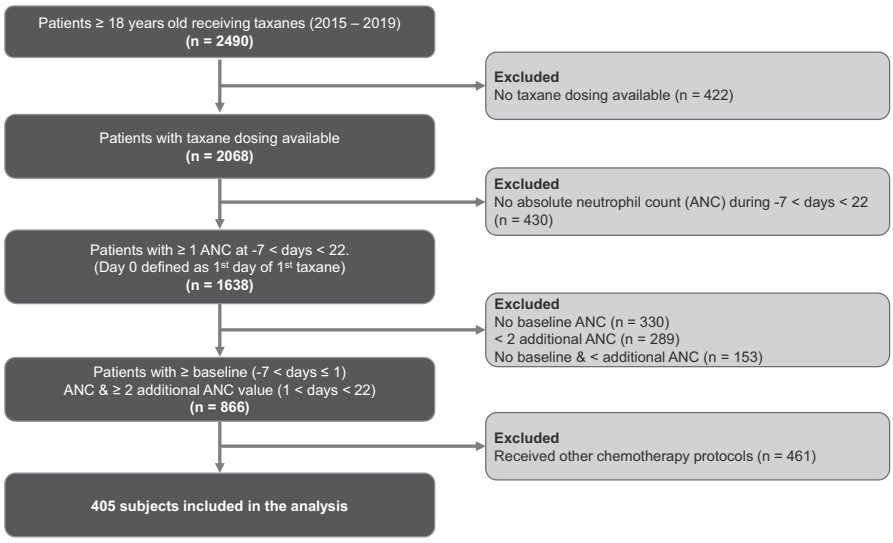


FIGURE 1 Flowchart of screening the eligibility of patients for inclusion in the final analysis.

TABLE 1 Baseline demographics and treatment characteristics for patients included in the population PK/PD modeling stratified by age group (total $n = 405$).

Characteristic	<70 years ($n = 319$)	≥70 years ($n = 86$)
Chemotherapy, *n* (%)		
Single weekly paclitaxel	144 (45.1)	23 (26.7)
Weekly paclitaxel/carboplatin	136 (42.6)	43 (50)
Every 3 weeks paclitaxel/carboplatin	39 (12.3)	20 (23.3)
Sex, *n* (%)		
Female	279 (87.5)	70 (81.4)
Male	40 (12.5)	16 (18.6)
Bilirubin level, μmol/L, mean (SD)[a]	8.4 (4.2)	9.2 (5.4)
Body surface area, m^2, mean (SD)[a]	1.8 (0.2)	1.8 (0.3)
Received antimicrobials, *n* (%)[b]		
No	267 (83.7)	76 (88.4)
Yes	52 (16.3)	10 (11.6)
Received growth factors, *n* (%)[b]		
No	296 (92.8)	78 (90.7)
Yes	23 (7.2)	8 (9.3)
Received steroids, *n* (%)[b]		
No	80 (25.1)	24 (27.9)
Yes	239 (74.9)	62 (72.1)
Albumin level, g/dL, mean (SD)[a]	3.7 (0.6)	3.3 (0.5)
Absolute neutrophils, $\times 10^9$ cells/L, mean (SD)[a]	7.4 (5.4)	6.9 (4.4)
Hemoglobin, g/dL, mean (SD)[a]	11.5 (1.9)	11.4 (1.9)
Platelet, $\times 10^9$/L, mean (SD)[a]	278 (109)	279 (119)
Race, *n* (%)		
Non-White	154 (48.3)	30 (34.9)
White	165 (51.7)	56 (65.1)
Cancer location, *n* (%)		
Breast	211 (66.1)	27 (31.4)
Non-breast	108 (33.9)	59 (68.6)

Abbreviations: *n*, number; PK/PD, pharmacokinetic/pharmacodynamic; SD, standard deviation.

[a]Baseline values.

[b]During first month of chemotherapy treatment.

demonstrate similar and adequate fitting of the longitudinal ANC data (Figure S6). Consequently, individual PD parameter estimates from the first approach were used for subsequent analyses steps.

Similar to observed values, mean model-predicted nadir ANC was 2.6×10^9 cells/L in the less than 70 years age group and 2.4×10^9 cells/L in the greater than or equal to 70 years age group. The mean nadir count in every 3 weeks paclitaxel/carboplatin treatment group was 2.09×10^9 cells/L compared to 2.81×10^9 cells/L and 2.45×10^9 cells/L in the weekly paclitaxel/carboplatin and the single weekly paclitaxel treatment groups. Figure 3 shows boxplots of predicted nadir ANC across age quantiles subdivided by chemotherapy regimen. The distribution of nadir ANC across the age quantiles within each regimen is similar. Figure 4 shows the percentages of administered of comedications in different age quantiles. The distributions of adjunct therapies, such as growth factors, and antimicrobials, are similar demonstrating a lack of age effect on paclitaxel-induced myelosuppression.

Figure 5a shows the scatterplot and correlation between observed and model-predicted nadir ANC and Figure 5b shows the correlation between observed, and model-predicted baseline ANC, which indicate adequate correlation between both values, although the model slightly underpredicts baseline ANC specifically at higher values.

Predictors of paclitaxel-induced myelosuppression

Table 2 shows the results of stepwise regression analysis to identify the predictors of paclitaxel-induced myelosuppression for the outcomes, namely, random effects of paclitaxel slope and MTT (the PD parameters) and model-predicted ANC. Baseline ANC was a significant predictor for paclitaxel slope where each unit increase in baseline ANC was associated with 0.01 increase in drug slope random effect given that other predictors are fixed (p-value < 0.001). In other words, patients who have higher baseline ANC will show more sensitivity of bone marrow to paclitaxel-induced myelosuppression. Further, each unit increase in baseline ANC was associated with 0.19×10^9 cells/L increase in nadir ANC (p-value < 0.001). Chemotherapeutic regimen type was associated with outcomes. Compared to every 3 weeks paclitaxel/carboplatin regimen, weekly paclitaxel/carboplatin and single weekly paclitaxel showed lower bone marrow sensitivity or slope (adjusted β coefficient $= -0.05$ and -0.16, respectively; p value $= 0.1$ and < 0.001, respectively). The use of steroids and growth factors were evaluated as predictors on the MTT parameter; however, the magnitude of the effect was not clinically meaningful (3% increase and 3.5% decrease, respectively). Therefore, they were not included in the

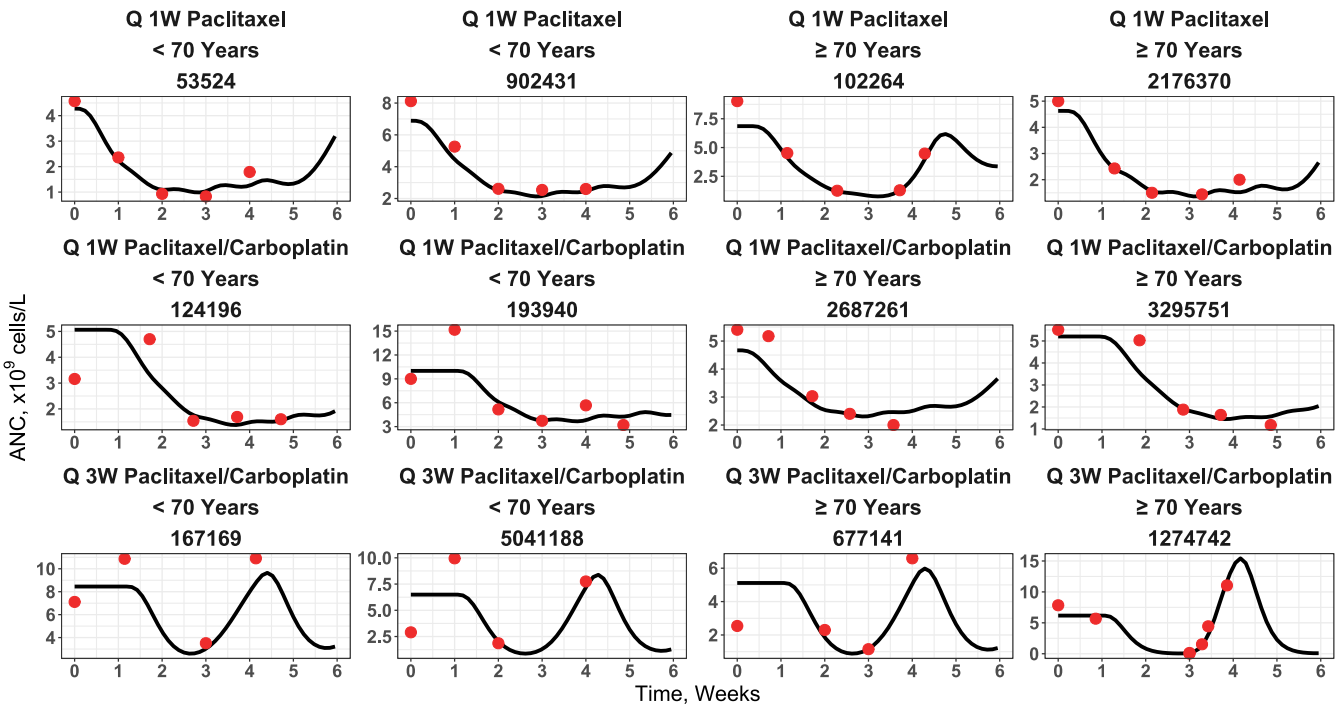
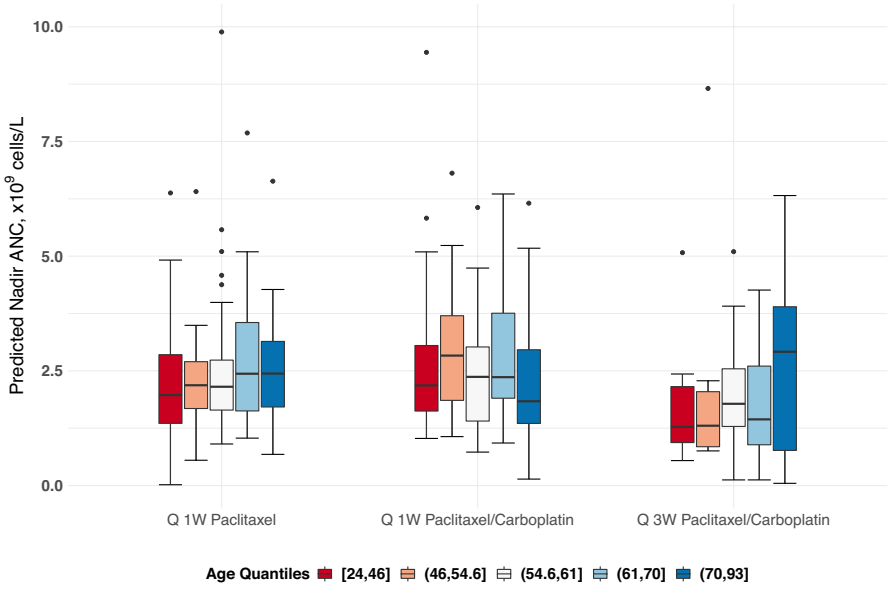


FIGURE 2 Representative individual fit profiles after estimating all pharmacodynamic parameters for absolute neutrophil count (ANC) across all studied regimens and age groups. Black lines represent model-based predictions and red dots represent observations.

FIGURE 3 Boxplot of predicted nadir absolute neutrophil count (ANC) across different age quantiles and subdivided by chemotherapy regimen.



final model. Age as a continuous covariate was not a significant predictor of any studied outcome.

DISCUSSION

This study has demonstrated that prior published PK/PD models can be leveraged and applied to EHR data to address key questions related to the real-world use of oncology therapeutics. Here, we have shown that among older patients treated in a community oncology care program, paclitaxel therapy is dosed to achieve similar average nadir ANC as younger patients. These results are supported by the considerable elderly population greater than or equal to 70 years of age (21.2% of the dataset). Furthermore, prescription patterns for growth factors, and antimicrobials are consistent across age quantiles, providing real-world evidence that age does not influence paclitaxel-induced myelosuppression.

The RWD have been applied to support clinical pharmacology decision making in oncology. This includes optimizing the cetuximab dose or supporting the use of

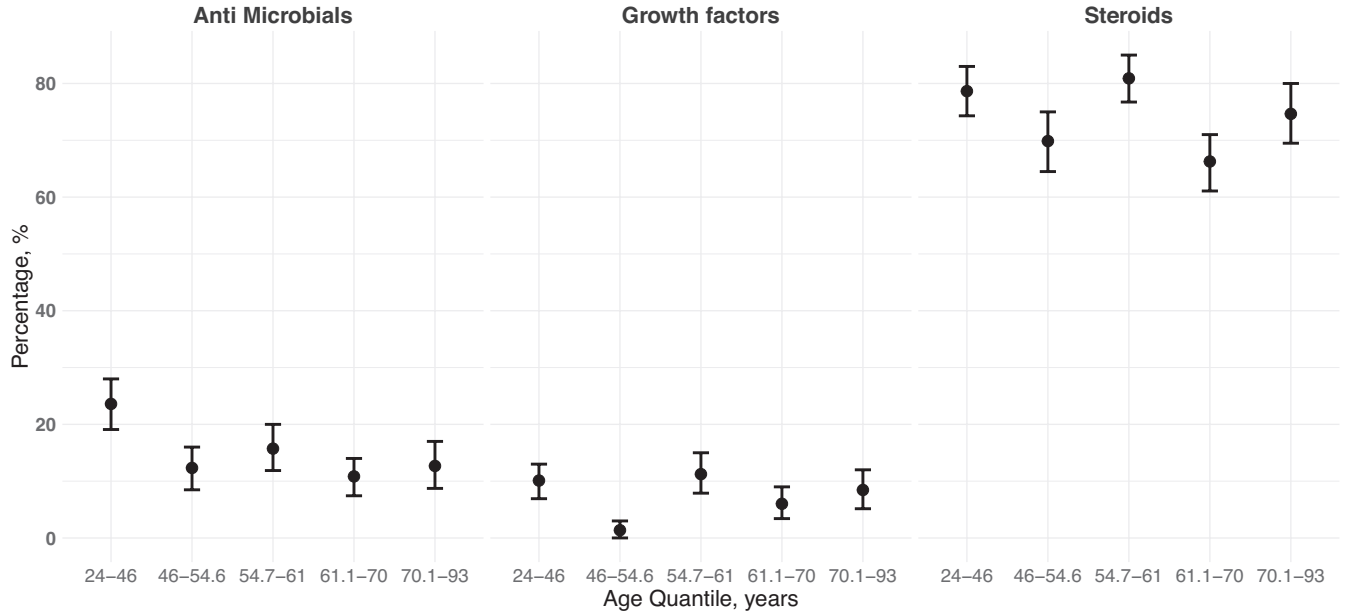


FIGURE 4 Percentages of administered comedications in different age quantiles.

palbociclib in the treatment of rare male breast cancer.[14,16] Paclitaxel clinical trials typically included patients who received a specific regimen of paclitaxel for a specific type of cancer. Moreover, most trials excluded the elderly and/or patients who received growth factors, and/or antimicrobials due to active infection.[23,24,27,31–34] Crombag et al.[22] pooled data from four clinical trials and one prospective observational study to create a heterogeneous dataset ($n = 300$) to study the predictors of paclitaxel-induced myelosuppression, albeit, with no information reported on the prescribed comedication. Although pooling of clinical trial data for heterogeneity is an option, there are often several challenges associated with it such as: (i) cost of conducting the clinical trial which could typically range from $3.4 million to $21.4 million depending on the trial size[35]; (ii) logistics associated with sharing of clinical trial data and collaboration between multiple investigators; and (iii) different trial objectives that may affect collection of common relevant data variables necessary for modeling. Although retrieving and preparing EHR data for analysis is onerous, the RWD has the advantage of readily available, routinely collected clinical care information across a heterogeneous patient population and eliminates selection bias. This study utilized and analyzed a curated database of 405 heterogeneous patients based on clinical, disease, and demographic characteristics from an EHR pool of 2490 patients.

Using EHR data for PK/PD modeling could be challenging due to nonstandardization of data entry and structure. Simple manual curation methods or complex algorithms and software could enhance the retrieval, curation, and processing of large real-world datasets.[6] Although heterogeneity of information is an imperative aspect of RWD, given the retrospective nature of the EHR data, sparse (i.e., PK/PD variables) and missing information (i.e., dosing records) pose challenges in PK/PD model development and parameter estimation. On the other hand, clinical trial data are prospectively collected with specific objectives and typically contain complete information on variables (i.e., accurate dosing records) with rich PK/PD sampling, thus enabling robust PK/PD model development.[26–28] In this study, we overcame the challenges of EHR data by using appropriate screening criteria (i.e., at least three ANC measurements [one baseline value and additional two measurements]) and leveraged prior published PK/PD models to precisely estimate the parameters of the ANC model. Additionally, therapeutic drug monitoring of paclitaxel was not part of routine clinical care, hence the PK information for paclitaxel was not available for the EHR cohort. Consequently, we relied on a published population PK model for paclitaxel with relevant covariates to approximate individual concentrations.[26] To summarize, both EHR and clinical trial datasets complement each other to fill the knowledge gaps to optimize medical care in real world settings. The clinical trial data enables development of PK/PD models and characterizes exposure-response relationships, whereas EHR data could provide more insights into covariate effects or patient specific factors, which might not be captured during clinical trial data collection.

In our analysis of EHR data, the PD parameter estimates from the myelosuppression PK/PD model matched the reported estimates from clinical trial data.[27,28] However, the drug effect parameter estimates, namely paclitaxel and

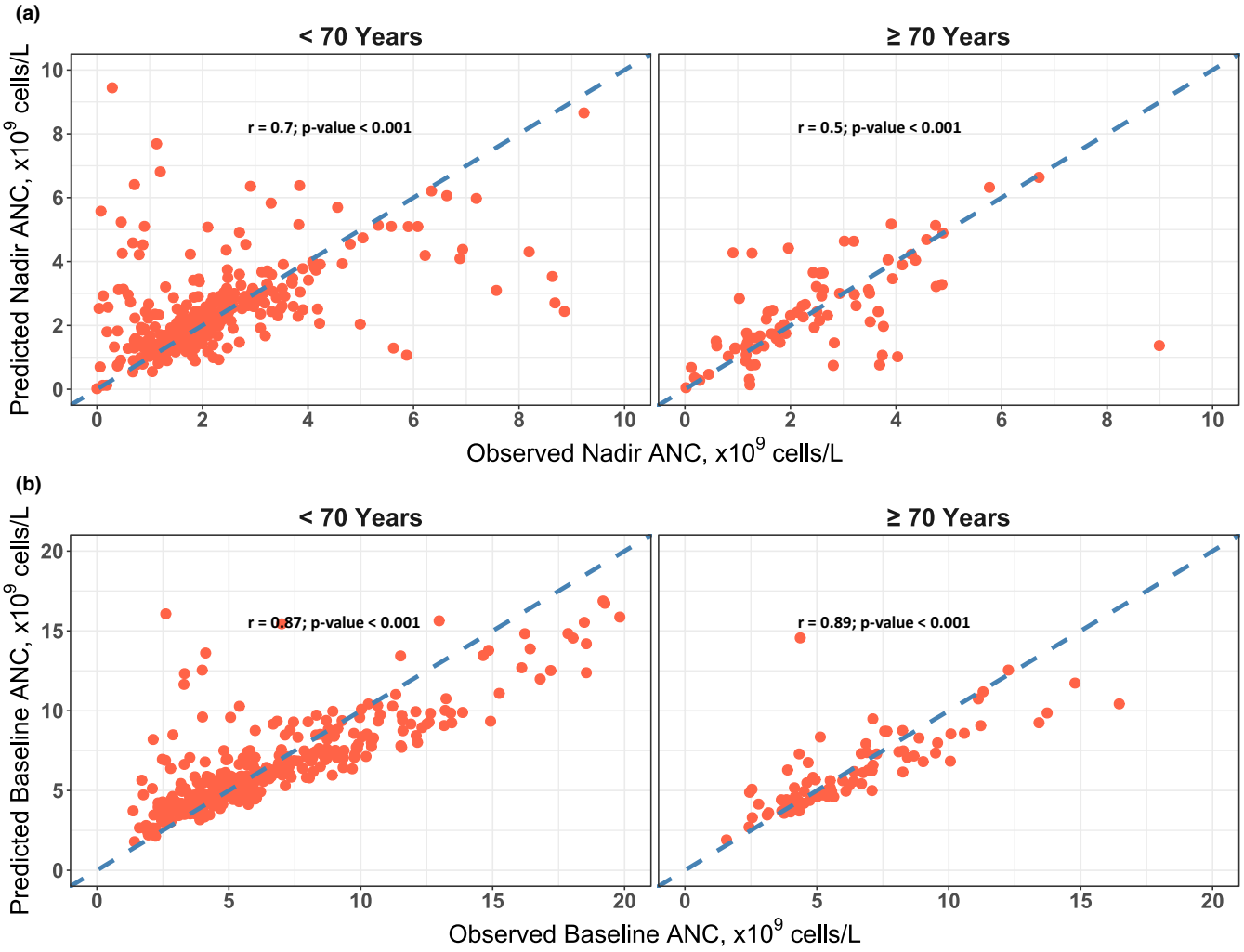


FIGURE 5 (a) Correlation between model-predicted and observed nadir absolute neutrophil count (ANC) divided by age groups. (b) Correlation between model-predicted and observed baseline ANC divided by age groups. The dashed blue line represents the line of unity.

carboplatin slopes, were 2.8 and three-fold higher than the reported values, respectively. The reason could be that we used typical mean PK parameters to simulate the drug concentration in patients (because the individual PK profiles were not available in our dataset), which was then incorporated in the PK/PD model estimation in contrast to previous studies that relied on post hoc individual PK parameters. Because the individual PK parameters are log-normally distributed, using mean values will result in lower exposures than using the post hoc estimates, hence, the slope estimate will be higher to maintain the same exposure-response relationship. In conclusion, PD parameter estimates from EHR data were similar to literature values and predictions matched those obtained from external validation approach.

The association between age and paclitaxel-induced myelosuppression has been a subject of extensive research where several studies have shown conflicting results and limitations in the analysis. The elderly are often excluded from clinical trials; therefore, using EHR data can provide an opportunity to explore this population, which may be useful for answering clinical care-related questions, such as dosing in the elderly. Our analysis included considerable elderly population (21.2% ≥70 years, also, including ≥80 years proportion). The American Society of Clinical Oncology moderately recommends the prophylactic use of growth factors for aggressive lymphoma in elderly patients who receive chemotherapy for curative intent.[36] Interestingly, our exploratory analysis of the distribution of use of growth factors, and antimicrobials, which are administered to treat myelosuppression complications, revealed that the distributions are consistent across all the age quantiles which provides real-world evidence of the lack of age effect on paclitaxel-induced myelosuppression.

In addition, multivariable regression analysis showed that age was not associated with the outcomes, namely paclitaxel slope, MTT, and model-predicted nadir ANC, which is consistent with the findings of Crombag et al.[22] However, the authors did not include results for nadir

TABLE 2 Results of stepwise multivariable regression analysis for the significant predictors of pharmacodynamic parameters and clinical outcomes at $\alpha = 0.001$ (n total = 405).

Outcome	Significant predictor	Unadjusted β coefficients[a] (95% CI)	*p*-value	Adjusted β coefficients[a] (95% CI)	*p*-value
Paclitaxel slope (SLOPE)[b]	Baseline ANC	0.01 (0.006, 0.014)	<0.001	0.01 (0.007, 0.015)	<0.001
	Regimen-weekly paclitaxel[c]	−0.14 (−0.2, −0.08)	<0.001	−0.16 (−0.22, −0.01)	<0.001
	Regimen-weekly paclitaxel/carboplatin[c]	−0.03 (−0.01, 0.03)	0.3	−0.05 (−0.11, 0.01)	0.1
Nadir ANC[d]	Baseline ANC	0.19 (0.16, 0.22)	<0.001	0.19 (0.15, 0.22)	<0.001

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval.

[a]β coefficient is the linear regression slope for continuous outcomes (SLOPE & nadir ANC).

[b]Studied predictors included: age, sex, baseline body surface area (BSA), baseline ANC, cancer location, self-reported race, chemotherapy regimen, receiving steroids, growth factors or antimicrobials, baseline bilirubin and baseline estimated glomerular filtration rate (EGFR).

[c]Reference is every 3 weeks paclitaxel/carboplatin.

[d]Studied predictors included: age, sex, baseline body surface area (BSA), baseline ANC, cancer location, self-reported race, regimen, baseline bilirubin, and baseline estimated glomerular filtration rate (EGFR).

ANC, a relevant clinically meaningful outcome.[22] Juan et al.[24] showed that the weekly paclitaxel regimen was well tolerated in 57 elderly patients with 1.8% of patients experiencing grade III/IV neutropenia, which was a way to assess neutropenia severity in clinics in the past, but the analysis did not include a control arm. Another retrospective study by Nakamura et al.[37] showed that the incidence of grade III/IV neutropenia was similar between young and elderly patients receiving every-3-weeks single paclitaxel regimen without adjusting for other confounders. In contrast, paclitaxel drug label shows that across multiple clinical trials with different paclitaxel-containing regimens and type of cancer, the elderly tend to experience grade III/IV neutropenia more frequently than the younger group, however, this trend did not reach statistical significance in most studies.[20] Additionally, a prospective analysis conducted by the Cancer and Leukemia Group B demonstrated that the elderly showed statistically significant lower nadir ANC and higher incidence of grade III neutropenia in the elderly in univariate analysis but no further multiple regression analysis was conducted.[23] Based on this study and other studies, the association between age and paclitaxel-induced myelosuppression is not well-established and clinicians could potentially maintain the current practice in managing elderly patients receiving paclitaxel-containing therapy. Of note, our analysis focused on the first cycle of chemotherapy, which has been well-supported by multiple studies as a predictor of myelosuppressive complications later in the therapy.[38–40] However, this should not preclude the hypothesis that the elderly may be more likely to experience myelosuppression in later chemotherapy cycles due to cumulative risk from earlier cycles.

Using EHR data for the current analysis entailed some challenges. As mentioned earlier, individual PK information was not collected during routine clinical practice and was not available for all patients. Because the established myelosuppression PK/PD model requires exposure information to be linearly linked to the PD model, we leveraged the previously published population PK model for carboplatin and PK model for paclitaxel where age, BSA, bilirubin, and sex were used to explain BSV in paclitaxel PK parameters to approach individual exposures as close as possible.[26,27] In addition, our data extraction and mining methods were insensitive to perform a more in-depth individualized analysis (we initially identified >2000 patients only to then analyze ~400 patients) or to identify additional covariates (Eastern Cooperative Group Performance Status) or clinical outcomes (as we focused on the first cycle nadir ANC rather than actual treatment outcomes like progression-free survival or emergency department visits and hospitalization rates over the course of the regimen).

In conclusion, we successfully fit data from EHR using prior published PK/PD models developed for paclitaxel, carboplatin, and myelosuppression based on clinical trial data. This indicates the robustness of these models to handle data obtained from heterogeneous populations. Across the age quantiles, growth factors and antimicrobials were used consistently, and the effect of age on paclitaxel-induced myelosuppression was not observed. Hence, the elderly can be managed according to current clinical practice standards. In the future, more efforts should be directed toward developing tools for automating and standardizing data extraction from EHR and data processing.

By utilizing these tools, therapeutics can be optimized, especially for vulnerable populations.

AUTHOR CONTRIBUTIONS

A.M.S. wrote the manuscript. A.M.S., M.L.M., and M.G. designed the research. A.M.S., E.D., S.K., M.L.M., and M.G. performed the research. A.M.S. and E.D. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

M.L.M. is employed by and holds equity in Intellia Therapeutics, Inc. All other authors declared no competing interests for this work.

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